Computational Methods for Conformational Analysis of Unsymmetrical 1,3-Diamines: 3-Aminotropanes

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ABSTRACT: A comparative study has been performed to evaluate the ability of a range of computational theories to predict the relative basicity and the conformations of diamine systems. Specifically, molecular mechanics (MM3), semiempirical (AM1), and *ab initio* (Hartree–Fock) methods have been used in the conformational analyses of unprotonated, monoprotonated, and diprotonated 3-aminotropanes, a pair of isomeric 1,3-diamines. Use of the molecular mechanics force field, with the recently determined parameter set for protonated amines, affords results that are in agreement with experimental data, when corrected for water solvent (by setting the dielectric constant to 80). *Ab initio* and semiempirical calculations, in contrast, give inconsistent and incorrect results.
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Keywords: molecular mechanics; MM3; semiempirical; AM1; AM1-SM2; *ab initio* calculations; Spartan; Gaussian94; 1,3-diamines; protonated amines; 3-aminotropane

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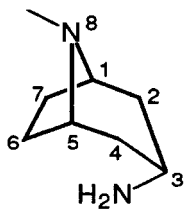
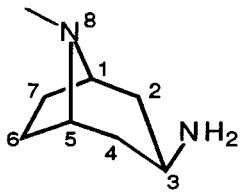
Introduction

Computational methods have become increasingly important in understanding biological mechanisms, and in the design of potential biochemical probes, imaging agents, and drugs. Because *ab intio* methods require significant amounts of computer time and memory, semiempirical (e.g., the Hamiltonian AM1) and molecular mechanics (e.g., MM3) methods have been the computational tools of choice for larger chemical systems. Until recently, however, these methods have lacked specific atom types to describe protonated nitrogen atoms. As a result, computational studies of nitrogen-containing compounds, as they exist in a physiological environment, where nitrogen atoms may be protonated, have relied on the use of uncharged amines as model compounds. To fill this void we have developed the required parameters for ammonium ions and amino groups in the MM3 force field.[1] The new parameters were found to reproduce the vibrational spectra and molecular geometries for a series of aliphatic amines.

In the course of our investigations of the molecular features responsible for the actions of polyamines, we had become particularly interested in the protonation sites and conformations of unsymmetrical 1,3-diamines. Using the conformationally constrained 3α- and 3β-aminotropanes (α and β) as model compounds, we determined by NMR, in aqueous solution,[2] that the lowest energy conformation is chair-like with the *N*-methyl group in equatorial position, in the diprotonated, monoprotonated, and unprotonated species. In the diprotonated form, the experimental energy difference between the equatorial and axial *N*-methyl conformers was found to be 1.2–1.3 kcal/mol.[2] In addition, we were able to determine that, in each case, the tertiary amino group of 3-aminotropane is more basic than the primary amino group. Use of these observations as a reference point afforded us the opportunity to examine the predictive value of computational methods with respect to this 1,3-diamine system.



α



β

Methods

To assess the quality of the MM3 ammonium parameters,[1] the results of MM3(96), *ab initio*, and semiempirical methods, as applied to 3-aminotropanes α and β, in the gas phase, were obtained. Further validation was sought by comparing the performance of MM3(96) and semiempirical methods for α and β in aqueous medium.

Molecular structures were constructed and subsequently optimized at the HF/6-31G* level in SPARTAN,[3] supplemented by frequency calculations done with the Gaussian94[4] program. The frequency calculations were primarily used to obtain zero-point vibrational energy (ZPVE) corrections; however, the data also provided insight to the positions of the various conformations on a potential energy surface. Thus, the Hartree–Fock values reported in this work include ZPVE (Tables I and II). Gas-phase AM1 and aqueous solvation AM1-SM2 semiempirical methods were used to optimize α and β in SPARTAN. For molecular mechanics optimizations MM3(96)[5] was augmented by the ammonium ion parameters,[1] and used with dielectric constants of 1.5 and 80, to reproduce gas phase and aqueous solvation, respectively. All calculations were performed on Silicon Graphics Indigo2 workstations. The absolute energy value for each minimum energy conformation, as obtained using each computational method, are reported in Tables I and II for unprotonated, monoprotonated, and diprotonated α and β, respectively. Relative energy differences, which are used in the conformational analysis, are summarized in Table III.

Various conformations that are not stationary points were examined within one or more of the computational paradigms. For example, boat conformations of 3β-aminotropane in which the *N*-methyl substituent is axial are highly unstable due to crowding within the boat. Therefore, a few conformations could only be optimized with the aid of a constraint (one fixed interatomic distance). Although such constraints preclude absolute optimization, they provide useful approximations for data evaluation. Values obtained using constraints are noted in Table III. Additionally, there were a

TABLE I.
Absolute Energies of the 3α-Aminotropane Minimum Energy Conformers.

Species	HF / 6-31G*[a]	MM3(96)[b,c]	MM3(96)-dc80[b,c]	AM1[d,c]	AM1-SM2[d,c]
Unprotonated	−420.877203	36.6703	36.7670	0.636097	−4.449287
Monoprotonated	−421.263151	21.7201	24.0108	142.197619	86.626138
Diprotonated	−421.484587	68.1990	24.0129	370.162343	192.554752

[a] Hartree–Fock energy; hartree.
[b] Steric energy.
[c] kcal / mol.
[d] Heat of formation.

TABLE II.
Absolute Energies of the 3β-Aminotropane Minimum Energy Conformers.

Species	HF-6 / 31G*[a]	MM3(96)[b,c]	MM3(96)-dc80[b,c]	AM1[d,c]	AM1-SM2[d,c]
Unprotonated	−420.880137	34.0274	33.7967	−0.204989	−7.222938
Monoprotonated	−421.267132	18.6282	21.0084	139.848121	82.961357
Diprotonated	−421.493929	61.8778	20.0067	367.630409	187.532160

[a] Hartree–Fock energy; hartree.
[b] Steric energy.
[c] kcal / mol.
[d] Heat of formation.

TABLE III.
Relative Energies of 3-Aminotropanes.[a]

	Calculated for									
	α[b]					β[b]				
Structure	HF / 6-31G*	MM3(96)	MM3(96) dc80	AM1	AM1-SM2	HF / 6-31G*	MM3(96)	MM3(96) dc80	AM1	AM1-SM2
1a	0.00	0.00	0.00	0.76	1.92	0.00	0.00	0.00	0.00	2.31
1b	3.63	2.07	2.03	0.00	0.00	8.71	6.15	6.65	6.11	X
1c	1.02	1.37	1.31	1.82	2.59	0.25	1.15	1.31	0.30	0.00
1d	6.40	6.33	6.25	4.58[c]	X[d]	X[d]	X[d]	X[d]	X[d]	X
2a	0.00	0.00	0.00	0.00	8.87	2.15	0.00	0.00	1.90	10.78
2b	7.78	6.44	4.61	3.62	11.82	0.00	1.68	9.76	0.00	8.41
2c	14.93	14.77	11.87	3.66	2.10	13.77	12.78	10.86	4.78	0.93
2d	15.82	14.70	12.87	5.26	0.00	9.59	15.08	16.76	0.99	0.00
2e	16.57	16.19	13.10	6.34	4.41	15.68	14.99	12.13	8.00	4.69
2f	20.72	19.73	17.00	10.80[c]	5.67[c]	X[d]	X[d]	X[d]	X[d]	X[d]
2g	2.31	1.22	1.48	2.29	10.58	4.33	2.30	1.49	4.02	12.43
2h	X[d]	X[d]	X[d]	6.36	13.04	X[d]	12.82	X[d]	14.75[c]	X[d]
3a	0.00	0.00	0.00	0.00	X[d]	0.00	2.37	0.00	0.00	0.00
3b	3.29	3.50	3.52	2.18[c]	13.78	X[d]	X[d]	X[d]	18.91[c]	X
3c	1.87	0.05	1.40	2.06	0.00	2.29	0.00	1.32	2.38	1.59
3d	X[d]	2.27	6.63	7.64[c]	5.95[c]	X[d]	X[d]	X[d]	X[d]	X[d]

[a] kcal / mol.
[b] See Figures 1 and 2.
[c] Constrained optimized values.
[d] Unstable, non-stationary points.

few conformations for which a constraint was not sufficient to allow even partial optimization. In these cases, we performed single-point calculations based on the Hartree–Fock-optimized geometries, if available, to assess the relative magnitude of the energy difference between the unstable conformations and the minimum energy conformer. Because these quantities are not physically meaningful, they are not included in the discussion, and have simply been noted as ''X'' in Table III.

Discussion

This study of 3α- and 3β-aminotropanes was designed to test the quality of the MM3(96) ammonium ion parameter set[1] and to explore the ability of molecular mechanics and semiempirical methods to reproduce experimental results. In light of the fact that the MM3(96) ammonium ion parameter set[1] had been developed for gas phase species using *ab initio* data, this study includes gas phase results from Hartree–Fock and semiempirical AM1 calculations. For comparison with experimental results, in water as a physiologically relevant medium, the study focused on MM3(96) with a dielectric continuum of 80 and on AM1-SM2 calculations.

The 3α- and 3β-aminotropanes may exist in either chair or boat form, and may have the *N*-methyl group axial or equatorial in the piperidine ring, as shown in Figures 1 and 2 (for α and β, respectively). Ring inversion interconverts the chair and boat conformations of the piperidine ring whether or not the species are protonated. For example, for the chair α**1a**, ring inversion leads to the boat α**1b**, and results in converting the axial 3-amino group to an equatorial substituent. Similarly, the monoprotonated chairs α**2a**, α**2c**, α**2e**, and α**2g** interconvert with the analogous boats

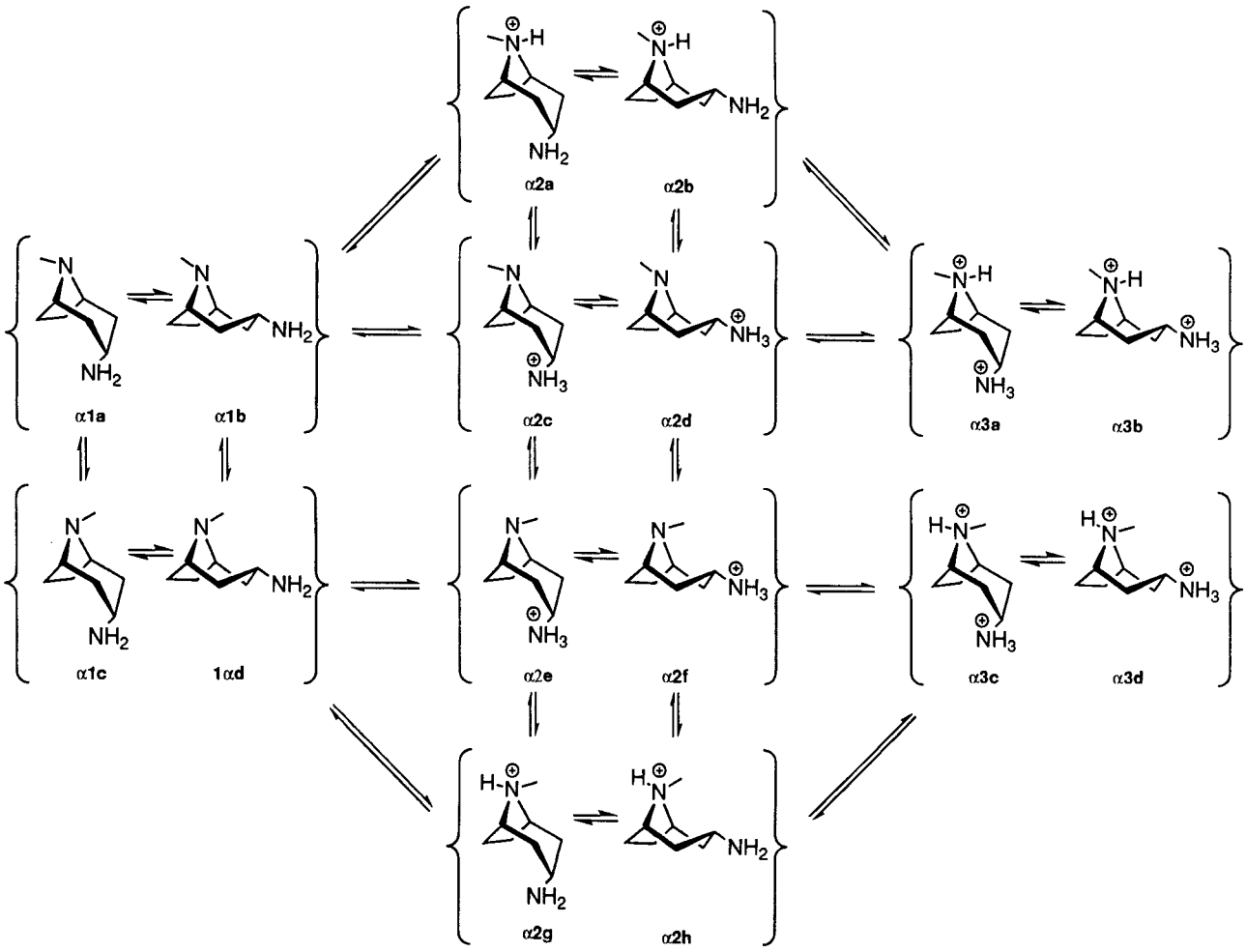


FIGURE 1. Interconversion of 3α-aminotropanes.

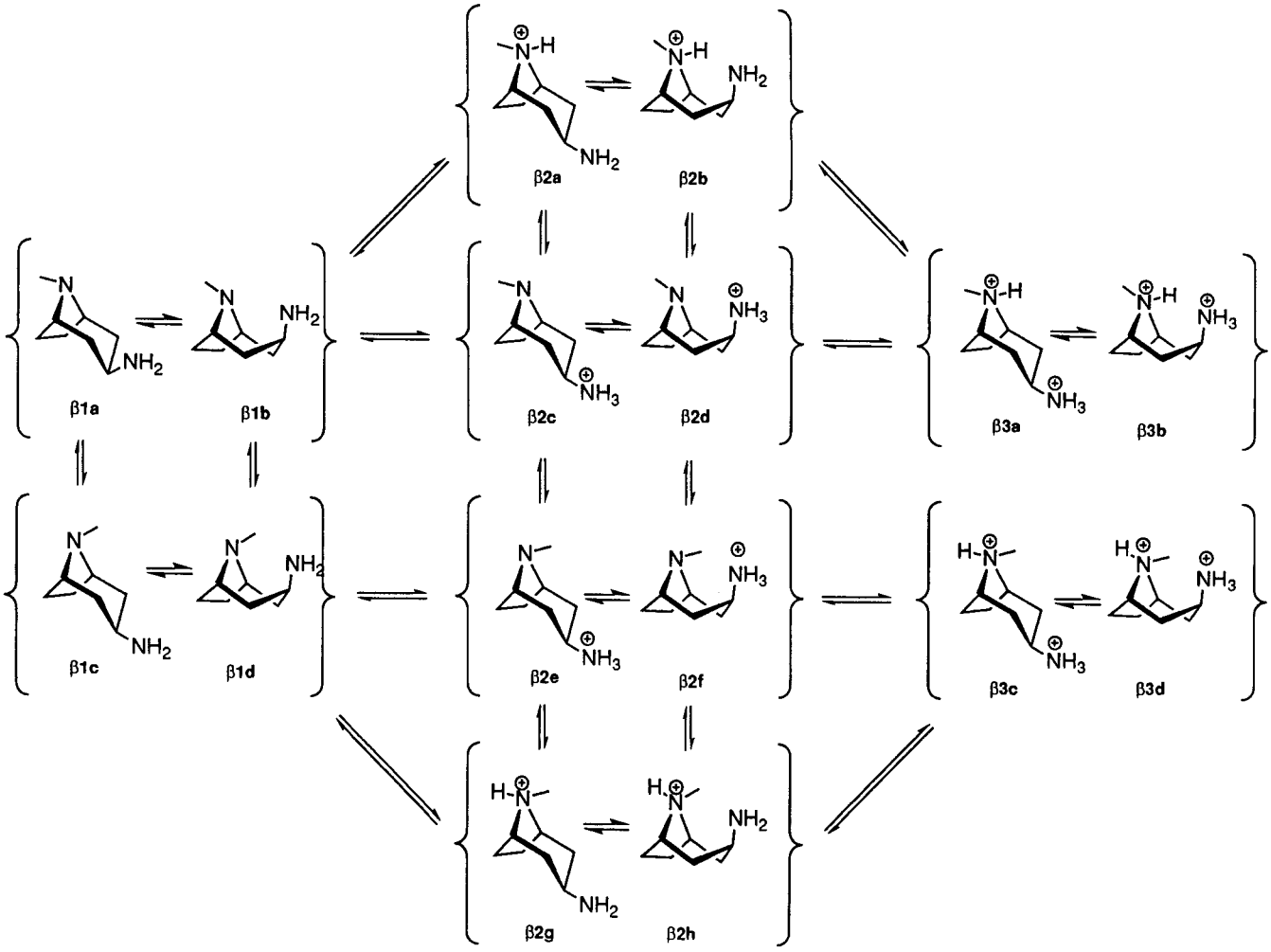


FIGURE 2. Interconversion of 3 β-aminotropanes.

α**2b**, α**2d**, α**2f**, and α**2h**, as do the diprotonated chairs α**3a** and α**3c** with the boats α**3b** and α**3d**. Analogous interconversions are possible for 3β-aminotropane (β). However for β, boat conformations may be destabilized by severe steric crowding, resulting from the presence of the axial 3-amino substituent. On the other hand, the axial 3-amino group may stabilize the boat conformation by internal hydrogen bonding, acting as a hydrogen atom donor, as in β**2d**, and as a hydrogen bond acceptor, as in β**2b**. In fact, these two monoprotonated species may not be discrete (Fig. 3).

Unless the bridge nitrogen is protonated, inversion at N(8) may occur, allowing equilibration of the *N*-methyl group between equatorial and axial positions. Therefore, *N*-methyl interconversion can take place in the unprotonated chair (**1a** ⇌ **1c**) or

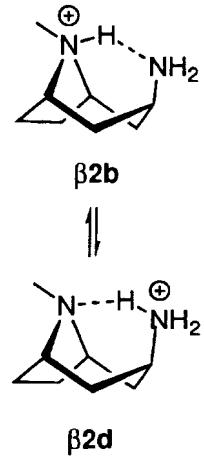


FIGURE 3. Boat forms of monoprotonated 3β-aminotropane with internal hydrogen bonds.

boat (**1b** ⇌ **1d**), as well as in species in which only the 3-amino group is protonated (**2c** ⇌ **2e** and **2d** ⇌ **2f**). On the other hand, because nitrogen inversion cannot occur when the bridge nitrogen is protonated (**2a** and **2g**, **2b** and **2h**, **3a** and **3c**, **3b** and **3d**) equilibration of the *N*-methyl group between equatorial and axial positions can only take place by a deprotonation/inversion/reprotonation process. This situation obtains for both 3α- and 3β-aminotropanes, and is shown in Figures 1 and 2.

UNPROTONATED 3-AMINOTROPANES

For unprotonated 3β-aminotropane, four of the five computational methods used indicate that the chair conformation with an equatorial *N*-methyl group (β**1a**) is the global energy minimum; the calculated energy differences between conformations are in general agreement with expectations. Specifically, molecular mechanics methods predict an equatorial *N*-methyl substituent to be preferred to an axial *N*-methyl group by 1.2–1.3 kcal/mol (β**1a** vs. β**1c**). The energy differences calculated using Hartree–Fock and AM1, although qualitatively consistent with the molecular mechanics result, are quite small (0.2–0.3 kcal/mol). Conflicting results are obtained by the AM1-SM2 model, which predicts β**1c**, with an axial *N*-methyl substituent, to have a ΔH_f at least 2.3 kcal/mol lower than the equatorial form. Consistent with expectations based on steric considerations, the calculations indicate that the boat β**1b** is destabilized relative to the chair β**1a**, by 6.1–8.7 kcal/mol.

Both semiempirical methods, AM1 and AM1-SM2, give an unexpected result for the unprotonated α isomer. In this case, the semiempirical calculations predict a boat conformation (α**1b**) to be the low-energy structure. Although stabilization of the boat conformation might be attributable to intramolecular hydrogen bonding and/or medium effects, neither of these factors are supported by our results. Thus, intramolecular hydrogen bonding is precluded in conformation α**1b** because the N(3) protons are oriented away from N(8), and the calculated stability of the boat conformation can not be attributed to medium effects because both AM1 and AM1-SM2 predict this minimum. Moreover, the semiempirical predictions do not conform to our experimental results.[2] On the other hand, *ab initio* and MM3 methods are in agreement with each other and with experimental results.[2,6] Specifically, chair conformation α**1a** is the minimum energy structure, 1.0–1.4 kcal/mol lower than the chair conformation with an axial *N*-methyl group α**1c**, and 2.0–6.4 kcal/mol lower than either boat conformation. These are in reasonable agreement with the equatorial/axial preference (*A*-value) of 2.4 kcal/mol[6] reported for *N*-methylpiperidine when one keeps in mind that the tropane skeleton, *gauche* interactions of the equatorial *N*-methyl group with the ethylene bridge are likely to decrease the *A*-value. As expected, the least stable conformation is calculated to be α**1d**, a boat conformation with an axial *N*-methyl group.

MONOPROTONATED 3-AMINOTROPANES

Computational results for the monoprotonated α isomer largely agree with expectations and experiment. With the exception of the AM1-SM2 model, each of the methods predicts that the tertiary amino group is protonated in preference to the primary amino group, and that a chair-like conformation with an equatorial *N*-methyl substituent (α**2a**) is the low-energy species. The analogous structure in which the primary amino group is protonated (α**2c**) is predicted to be significantly higher in energy according to Hartree–Fock and molecular mechanics results (> 10 kcal/mol). AM1-SM2 calculations, in contrast, predict a boat conformation that is protonated on the primary nitrogen (α**2d**) to be at minimum energy. The magnitude of the preference for this boat conformation of monoprotonated α is striking, as α**2d** is 8.9 kcal/mol lower in energy than the experimentally validated minimum α**2a**. This result cannot be explained by internal hydrogen bonding, as the equatorial position of the 3-amino group in boat conformations of α precludes such an opportunity. Additionally, although the second-lowest energy structure predicted by AM1-SM2 for this isomer is a chair conformation with an equatorial *N*-methyl substituent, it is not α**2a**—rather it is the primary protonated species α**2c**.

For monoprotonated 3β-aminotropane, both *ab initio* and AM1 calculations indicate the boat conformation β**2b** has the lowest energy. A possible explanation may be that the steric strain associated with the boat conformation is compensated for by internal hydrogen bonding between the protonated piperidine nitrogen and the axial amino group. If this hypothesis were correct, the complementary boat conformation β**2d**, in which the 3-amino group is protonated (rather than the piperidinium nitrogen), would also be preferred over the chair structures β**2c** and β**2e**. This is, in fact, found by the Hartree–Fock and AM1 calculations

(Table I). On the other hand, stabilization of the boat conformations β**2b** and β**2d** by an intramolecular hydrogen bond appears doubtful based on the structural features of both Hartree–Fock- and AM1-optimized conformations of β**2b** and β**2d**. Thus, neither the +N(8)—H bond lengthening (0.011 Å for Hartree–Fock and 0.009 Å for AM1) in β**2b** relative to the chair β**2a**, nor the bond angle for a possible hydrogen bond (135.7° and 128.3° for Hartree–Fock and AM1, respectively), are consistent with a strong hydrogen bond, particularly one that would overcome boat strain and would lower the conformational energy by several kcal/mol relative to the most stable chair conformer. In addition, the large Hartree–Fock energy difference (9.6 kcal/mol) between β**2d** and β**2b** does not support the existence of an internally bonded species in which the proton is ''shared'' by the two amino groups (Fig. 3), although this possibility is suggested by the small energy difference between AM1-optimized β**2b** and β**2d** (1 kcal/mol). In light of the fact that the boat conformations β**2b** and β**2d** are discrete species in each computational model, the lowest energy structure predicted for monoprotonated β by AM1-SM2, β**2d**, in which the primary amino group is protonated, is surprising. It is also in contrast with experimental results.[2]

For monoprotonated 3β-aminotropane, the best agreement with experiment is obtained by MM3(96) calculations, with and without solvent correction. The molecular mechanics methods predict β**2a**, the chair form analogous to β**2b**, as the lowest energy monoprotonated species (Table I). As calculated by the solvated mechanics model (MM3-dc80), the chair conformer with an equatorial *N*-methyl group (β**2a**) is 1.5 kcal/mol lower in energy than the axial conformer (β**2g**), and significantly lower in energy than either boat conformer (about 10 and 17 kcal/mol). Thus, the MM3-dc80 results predict that the predominant monoprotonated species for both α and β aminotropane isomers will be the tertiary piperidinium ion in a chair conformation with an equatorial *N*-methyl group.

DIPROTONATED 3-AMINOTROPANES

Due to the compounded effects of steric crowding and proximate charges in boat forms of 3β-aminotropane, the structures β**3b** and β**3d** are highly unstable (Table III). In fact, they are not at stationary points on the potential energy surface according to any of the methods used in this work. Therefore, it is only necessary to consider the chair forms β**3a** and β**3c** in diprotonated β. For this aminotropane isomer, all methods, with the exception of gas-phase MM3, find β**3a**, which has an equatorial *N*-methyl substituent, to be the minimum energy diprotonated conformer, with equatorial/axial preference in the range of 1.3–2.4 kcal/mol. An inconsistent result is obtained by gas-phase MM3, which finds β**3c**, with an axial *N*-methyl group, as the minimum energy conformation. Destabilization of the equatorial conformation is primarily due to a difference in the charge-dipole term of the MM3-calculated energies, which is enhanced in the gas phase. In β**3a**, repulsion between the +N(8)—H bond dipole and protonated 3-amino group leads to a charge-dipole term that is about 5 kcal/mol higher than in β**3c**. This interaction should be decreased by solvent interaction and, indeed, application of the water-appropriate dielectric constant (80) to the MM3 calculations predicts β**3a**, with an equatorial *N*-methyl group, as the most stable conformation. The *A*-values for the methyl group on a protonated nitrogen, as predicted by all methods with the exception of gas-phase MM3, range from 1.3 to 3.4 kcal/mol, and, thus, are in general agreement with our experimental results,[2] and with published[6] results for protonated *N*-methylpiperidine (2.1 kcal/mol). Keeping in mind the gauche interactions between the equatorial *N*-methyl group and the ethylene bridge in tropanes, the energy difference between axial and equatorial *N*-methyl substituents in tropanes should be smaller than that for *N*-methylpiperidine. Therefore, the Hartree–Fock and AM1 calculated energy differences of 2.3 and 2.4 kcal/mol, although qualitatively correct, may be too large. In fact, the MM3-dc80 value of 1.3 kcal/mol is validated by our NMR results, where an energy difference of 1.3 kcal/mol has been calculated from the ratios of the integrated intensities of the *N*-methyl resonances in the proton NMR spectra of β in acidic water.[2]

Similar results are obtained for diprotonated α, with only a few anomalies. AM1-SM2 calculations fail to predict α**3a** as the minimum energy conformation; in fact, this conformation is unstable within the AM1-SM2 model. Gas-phase MM3 calculations do predict a chair conformation with an equatorial *N*-methyl group (α**3a**) to be the energy minimum, although the calculated equatorial/axial difference is only 0.05 kcal/mol. However, when the solvent correction is applied to MM3 by raising the dielectric constant to 80, an *A*-value of 1.4 kcal/mol is obtained. This result is in very good agreement

with the equatorial/axial preference of 1.2 kcal/mol, extrapolated from NMR data for α. Additionally, Hartree–Fock and AM1 methods predict equatorial preference of 1.9 and 2.1 kcal/mol. Although these values are close to the reported *A*-value of *N*-methylpiperidinium ion,[6] they may be too high, considering the additional steric strain in the tropane skeleton (see above). In addition, they do not show the same degree of agreement with experiment[2] as the solvated molecular mechanics calculations. These data strongly support the predictive value of the well-parameterized MM3 force field, when corrected with the dielectric constant of water. Although gas-phase MM3 calculations are often highly accurate, a dielectric correction can be extremely useful in situations where comparison is being made with an experimentally solvated species.

Conclusions

Both the experimentally determined relative basicities of the amino groups and the conformational preferences of unprotonated, monoprotonated, and diprotonated 3α- and 3β-aminotropanes in aqueous medium are well predicted by MM3(96), augmented by the ammonium ion parameters[1] and with dielectric constant 80. The quality of the MM3 results validates the recently developed ammonium parameters,[1] and highlights the importance of modeling solution-phase conditions when making comparisons to NMR data. The solvated semiempirical method AM1-SM2 fails to give results validated by experiment in this system.

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